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EXAMINER	
LEAVITT, MARÍA GOMEZ	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,201	EAKLE ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22 and 24-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22 and 24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-30-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of 10/18/2006 in response to restriction requirement is acknowledged. Applicant elected Group I, drawn to claims 1-22 and 24-29 and election of the following species, SEQ ID NO:5 as recited in claims 4, 5, 22 and 27 is acknowledged.

Therefore, claims 1-22 and 24-29 with elected species are pending for examination to which the following grounds of rejection are applicable.

Objections

Claim 1 is objected because of the abbreviation "BLV". An abbreviation should be spelled out at its first encounter in the claims.

Claims 4, 7, 22 and 27 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 4, 7, 22 and 27 introduce the limitation of sequences that hybridize to SEQ ID NO:5 and SEQ ID NO:7 under low stringency conditions. However, all sequences that hybridize are not necessarily dominant negative mutant BLV Rex protein encoding sequences.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 4, 7, 14-16, 19-22 and 24-27, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14-16, 19-21, and 24- 26, recite specific rages of amino acid sequences within the C-terminal of the BLV Rex protein, e.g., claim 14 recites the phrase "the C-terminal from amino acids 110-137", claim 15 recites the phrase "the C-terminal domain are from amino acids 115-125" and claim 16 recites the phrase " said C-terminal domain are from amino acids 119-120", however, the metes and bounds of the claim are not clearly determined since there is not reference sequence to provide context for these ranges.

Claim 21 recites the limitation "the host cell of Claim 19 ". However, claim 19 is drawn to a nucleic acid. Hence, there is insufficient antecedent basis for this limitation in the claim.

Claims 4, 7, 22 and 27 recite the limitation "low stringency ", because the art fails to specifically define what "low" is and the meaning can change with different artisans, the metes and bounds of the claim are not clearly determined.

35 USC 101-non-statutory subject matter

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-2, and 14-18 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory mater.

Claims 1 and 14 are drawn to a host cell comprising a genome. The specification discloses on page 7, lines 15-17, the meaning of "a host cell" as any eukaryotic cell, whether

located *in vitro or in vivo*. The scope of these claims, therefore, encompasses a human being, which is a non-statutory subject matter. As such, the recitation of the limitation "non-human" would be remedial. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112 – written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22, 24-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 5-6, 8-21, 24-26, 28-29 encompass a host cell comprising a genome, said genome comprising a gene encoding a transdominant negative Rex mutant of the bovine leukemia virus (BLV), which inhibits BLV replication. Applicant states that the term "transdominant rex mutant" (or TD rex mutant) refers to a nucleic acid sequence that encodes a protein or polypeptide that competes with or inhibits the function of a native Rex (wild type) protein or polypeptide" (p. 10, lines 22-24). A transdominant negative mutant of BLV when given the broadest reasonable interpretation encompass a genus of unspecified variants including

any deletions and/or substitutions and/or addition located in any unspecified genomic region, wherein the amino acid sequence of the BLV Rex protein encoded by the mRNA can be changed or unchanged resulting in mutations of transdominant negative Rex mutant, thus creating a gene sequence encoding a protein product which may have or not any functionality as to prevent other copies of the same wild type gene, which have not been mutated from functioning properly (p. 9, lines, 14-18). Additionally, claims 4, 7, 22 and 27 recite the limitation "low stringency conditions". This limitation when given the broadest reasonably interpretation encompass a DNA which hybridizes to the nucleotide sequence encoding SEQ ID NO:5, under low stringent conditions, comprising molecules which contain point mutations, addition and/or deletions which would result in encoding of a peptide that lacks any significant structure in common with SEQ ID NO: 5 and therefore any significant functionality in common with a transdominant negative Rex mutant of SEQ ID NO: 5.

The specification describes the construction of a BRex mutant designated BRex M4 (SEQ ID NO:5) and a BRex mutant of SEQ ID NO:7. The mutated amino acids in these constructs were selected after alignment of the BRex with homologous proteins sequences of Human T cell leukemia virus Rex protein (HRex) (p. 31, lines 19-30). Selection of residues to be mutated was based in the knowledge that amino acids of the regions 58-66 and 119-122 of the HRex were critical for Rex functionally and their disruption generated functional transdominant negative derivatives (see Fig 2, for illustrative purposes). Indeed, the BRex mutant M4 (SEQ ID NO:5) of the instant invention was generated by mutating aa residues 119 and 120 of the wild type BRex. This region is encompassed by the 119-122 aa residues of the wild type HRex which

is critical for its functionally (see, Score search results details for Application 10/764201. Alignment of wild type Brex and SEQ ID NO:5, e.g., mutated BRex).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant, provides only two examples of trans-dominant

negative mutants of BLV Rex, SEQ ID NO:5 and SEQ ID NO:7, able to inhibit BLV viral replication. Specifically, M4 mutant inhibits wild type Rex function as much as 80% in an *in vitro* assay which measured Rex-dependent export of unspliced RNA from the nucleus (p. 60, lines 18-26). However, no other specific teachings of a number of other species of trans-dominant negative mutant of BLV Rex able to inhibit wild type Rex function, other than SEQ ID NO:5 and SEQ ID NO:7, are disclosed. Moreover, the specification does not provide any disclosure as to what would have been the required structure for the claimed genus of trans-dominant negative mutant of BLV other than the amino acids analogous to those residues of the regions 58-66 and 119-122 found in HTLV Rex, which are found to generate inhibitory proteins.

Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., DNA sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, there are no other characteristic in addition to the functional discussed above is disclosed. Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera form each other.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a genus of transdominant negative BLV Rex mutants able to inhibit BLV replication, at the time the application was filed. Moreover, Applicant was not in possession of a genus of nucleic acid encoding a transdominant negative BLV Rex mutants able to hybridize to SEQ ID NO: 5 under low stringency conditions. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112 - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22, 24-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

A pseudotyped retroviral recombinant helper virus vector comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOS: 5, wherein said sequence encodes a transdominant negative mutant of the Bovine Leukemia Virus Rex, wherein the Rex coding region has a mutation in the C-terminal domain from amino acid 119-120, and when said recombinant helper retrovirus vector is introduced into an isolated host cell infected with wild type Bovine Leukemia Virus Rex, said host cell expresses a reduced level of Rex-dependent export of unspliced RNA from the nucleus and thus reduces baseline activity of Bovine Leukemia Virus replication relative to the levels of untransduced Bovine Leukemia Virus infected cells.

The specification does not reasonably provide enablement for claims directed to a host cell comprising a genome, said genome comprising a gene encoding a transdominant negative mutant of the BLV Rex protein or sequences that hybridize to SEQ ID NO:5 under low stringency conditions, wherein said nucleic acids encode a protein that inhibits BLV replication.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement

of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claim

The claims, when given the broadest possible interpretation, encompass a nucleic acid encoding a transdominant negative mutant of the BLV Rex protein, a retroviral vector comprising said genome, a host cell comprising said vector, wherein said nucleic acid encodes a protein that inhibits BLV replication. The claims are considered broad because the claims do not define the functional limitation of transdominant negative BLV Rex protein sequences or sequences that hybridize to SEQ ID NO:5 and the limitations can read on a genus of polypeptides that have a function of a transdominant negative mutant of BLV comprising any deletions and/or substitutions and/or addition located in any unspecified genomic region of the polypeptide that are not taught in the instant specification or known in the prior art. The specification provides insufficient data to enable claims directed to a host cell as broadly claimed. Thereby, specific issues including detailed domains required for a transdominant negative mutant gene of a target protein that inhibits replication of other copies of the wild type target protein gene, have to be examined and considered for patentability regarding the broadly claimed transdominant negative mutant of the BLV Rex protein.

Guidance in the Specification and working example

The instant specification discloses the construction of a BRex mutant designated BRex M4 (SEQ ID NO:5) and a BRex mutant of SEQ ID NO:7. The mutated amino acids in these constructs were selected after alignment of the BRex with homologous proteins sequences of Human T cell leukemia virus Rex protein (HRex) (p. 31, lines 19-30). Selection of residues to be mutated was based in the knowledge that amino acids of the regions 58-66 and 119-122 of the HRex were critical for Rex functionally and their disruption generated functional transdominant negative derivatives (see Fig 2, for illustrative purposes). Indeed, the BRex mutant M4 (SEQ ID NO:5) of the instant invention was generated by mutating aa residues 119 and 120 of the wild type BRex. This region is encompassed by the 119-122 aa residues of the wild type HRex which is critical for its functionally (see, Score search results details for Application 10/764201. Alignment of wild type Brex and SEQ ID NO:5, e.g., mutated BRex). Additionally, the specification discloses on page 60, lines 27-31, the establishment of a cell line that induces BLV replication, and on p. 61, lines 15-18, Figures 28 and 29 show that mutant M4 prevents induction of BLV replication in relation to wild type Rex or control. However, no other specific teachings are provided of any other representative number of a genus of nucleic acids encoding a transdominant negative mutant of BLV rex. The detail of the disclosure provided by the Applicant, in view of the prior Art, must encompass a wide area of knowledge to enable one of ordinary skill in the art at the time of the invention to practice the invention without undue experimentation. However, as it will be discussed below this undue experimentation has not been overcame by the as-filed application. Though, the specification teaches *in vitro* effects of Rex

and M4 on basal replication in host infected BLV cells, the broad aspects of a host cell comprising a gene encoding a transdominant negative mutant of the BLV Rex protein is not reasonably enable for the full scope embraced by the claims.

State of the prior art

The art of record teaches that it was well known in the art at the time the invention was made to use pseudotyped retroviral recombinant helper virus vectors comprising a nucleic acid sequence, wherein said sequence encodes a transdominant negative mutant, and said nucleic acid sequence further encodes a cell surface antigen. For example, Kingsman et al (US. Application No. 10/060,585) is an exemplified art that teach a vector system comprising and antibody and/or a nucleotide sequence ("NS") coding for a nucleotide of Interest ("NOI") which may optionally encode a protein of interest ("POI")(p. 1, [0021]; p. 5[0073] [0099]). The NOI or NOIs may be under the expression control of an expression regulatory element, usually a promoter or a promoter and enhancer. Additionally, Kingsman et al., recite that the viral vector system include a retroviral vector that can be pseudotyped by replacing the envelope with a heterologous *env* gene (p.5, [0068]). Kingsman et al., teach details of the retrovirus genomic structures and classification of these retroviruses including the oncogenic members, which are simple retrovirus, except for T-cell leukemia virus and bovine leukemia virus, which are complex oncogenic retroviruses (p. 2, [0041]). Moreover, Kingsman et al., disclose that the vector system may deliver the NS and/or NOI to a target cell. The target cell may be any host cell capable of expressing the antibody *in vivo* (or *ex vivo*) and/or the POI (p.8, [0111], [0112]). Further, Kingsman et al., cite a number of suitable NOIs including those of therapeutic and/or diagnostic application such as a transdominant negative mutant of a target protein, an antigen, a membrane

protein (p.6, [0092]). The NOI may be capable of blocking or inhibiting the expression of a gene in the target cell (p.6, [0080]). Thus, prior art teaches that a host cell can be transduced with a retroviral vector comprising a gene encoding a protein of interest under the control of a regulatory sequence wherein said expressed protein exhibit a functional activity in said host cell.

In so far as other retroviruses expressing a transdominant negative mutant inhibiting other copies of the same wild type gene from functioning properly, Bachmayer et al., teach a transdominant repressor of the function of the T-cell leukemia virus Rex (HTLV Rex) protein generated from a wild-type form of the HTLV Rex protein comprising mutations of at least one residue from amino acid position 59-121, particulary in any one of the amino acid positions 59, 60, 64, 65, 119, 120, and 121, generating proteins which exhibit trans-dominant repression of HTLV Rex protein function (p. 5, lines 45-57). Detailed construction and functional activity of HTLV Rex mutant is disclosed in Examples 1-5, pages 16-20. Further, Bachmayer et al., teach the prophylactic and therapeutic used of the invention particularly in retroviral diseases having genes similarly regulated to the HTLV including bovine immunodeficiency virus infection (p. 27, [0163] [0164]). Similar insight into gene homology but chemically distinct structure of HTLV and BLV retroviruses is taught by Oroszlan et al., by disclosing the homology of T-cell leukemia virus p24 and bovine leukemia virus (p. 1291, abstract and p. 1294, col. 1, paragraph 3 and 4). Thus, the art of record teaches specific mutations of the HTLV Rex wild type protein comprising at least one residue from amino acid position 59-121, preferentially at positions 59, 60, 64, 65, 119, 120, and 121. However, the prior art is silent about any transdominant negative mutant of the BLV Rex protein able to inhibit BLV replication.

Analysis of Quantity of Experimentation

As set forth above by the nature of the invention, the state of the prior art, neither the prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to employ a host cell comprising a gene encoding a transdominant negative mutant of the BLV Rex protein able to inhibit BLV replication as claimed, other than SEQ ID No. 5. Even when considering the sequence homology of the HTLV and BLV retroviruses as taught by Oroszlan et al., there is not predictability as to a direct correlation between functional mutants of HTLV Rex and BLV Rex. As the result, the issue of claiming broadly a genus of transdominant negative mutants of the BLV Rex protein and sequences that hybridize to SEQ ID NO:5 under low stringency conditions able to inhibit BLV replication have not been addressed by the as-filed specification. As such, given the unpredictability of the art and the lack of working examples in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the invention drawn to a host cell comprising a gene encoding a transdominant negative mutant of the BLV Rex protein able to inhibit BLV replication and to identify an enormous number of mutants as broadly or generically claimed, with a resultant recognition of those host cells comprising nucleic acids encoding proteins that inhibit BLV replication.

Conclusion

No claim is allowable

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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